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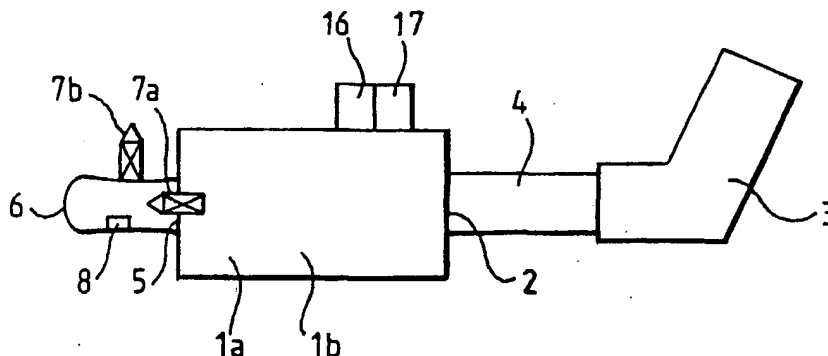
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(54) Title: DRUG DELIVERY APPARATUS



(57) Abstract: A drug delivery apparatus comprising: a drug delivery device for selectively delivering drug-laden air or air not laden with the drug; a sensor (4) for monitoring the breathing pattern of a patient; a controller (24) arranged to control the drug delivery device to deliver drug-laden air in pulses which begin when the patient is monitored by the sensor (4) to begin inhalation, the pulses having a duration which is adjusted by the controller (24) on the basis of the monitored breathing pattern of the patient; a feedback indicator (16) which indicates to a patient whether the monitored breathing pattern is effective for inhaling drug-laden air or not; a dose calculator (25) which calculates the dose delivered to the patient; and an indicator (17) which indicates to the patient when a desired dose has been delivered, whereby the apparatus is configured to deliver the full amount of the desired dose in at least 80 % of treatments.

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DRUG DELIVERY APPARATUS

The present invention relates to improved drug delivery apparatus, and to the use of improved drug formulations for delivery by the apparatus.

A number of drugs have been used for the treatment of patients with respiratory disorders. Antiproteinase inhibitors, such as Prolastin[®], are being studied and used in the treatment of inflammatory lung disease and approved for use in congenital emphysema. Prostacylins/prostacylin analogs, such as Iloprost, are used in the treatment of pulmonary hypertension. Mucoactive drugs, such as Pulmozyme[®] (recombinant, human DNase) and SuperVent^{®™} are used and studied in the treatment of patients with cystic fibrosis lung disease. Gamma interferon is being studied for use in the treatment of pulmonary fibrosis and tuberculosis. Immunosuppressants, such as cyclosporine, are being studied for the prevention of lung organ rejection. The Interferons, specific monoclonal antibodies, directed against tumor-associated antigens, receptors or oncogene proteins, and adenovirus-directed gene therapeutics, are used and studied as a treatment for various lung cancers.

Beta₂ adrenergic bronchodilators, such as Ventolin[®], Albuterol[®] and Salbutamol[®], are indicated for the prevention and relief of bronchospasm. Corticosteroids, such as Budesonide[®], are used in the treatment of inflammatory lung and reactive airways disease such as asthma. Surfactants, such as Exosurf[®], Survanta[®] and Surfaxin[™], are used to treat infant respiratory distress syndrome and are being studied as therapies in certain lung inflammatory diseases, such as chronic bronchitis and cystic fibrosis. Anti-infective agents [e.g., antibacterial (e.g., tobramycin); antifungal (e.g., AmBiosome[®]); and antiviral (e.g., Synagis[™], Virazole[®], the Interferons and vaccines)] are used to control pulmonary infections, particularly in subjects who are at risk, such as children, the elderly and the immunocompromised and in patients suffering for example with cystic fibrosis lung disease. These latter patients are prone to acute and chronic endobronchial infections, typically caused by the gram-negative bacterium, *Pseudomonas aeruginosa*. *Pseudomonas* infections are treated with the antimicrobial polypeptide, Colistin and the aminoglycoside antibiotic, Tobramycin.

WO 96/12471 discloses the use of an aminoglycoside formulation (Tobramycin) for aerosolisation. The formulation comprises from about 200 mg to about 400 of aminoglycoside dissolved in about 5ml of solution containing about 0.225% of sodium chloride. The formulation has a pH of between about 5.5 to 6.5 and is administered by aerosolisation. This formulation suppresses and inhibits at least 95% of susceptible bacteria in the endobronchial

space of a patient suffering from the endobronchial infection.

Various drug delivery apparatus are suitable for delivering such drugs in atomised form. For example, a jet-type nebuliser is disclosed in WO 96/12471 as being suitable for aerosolisation of the aminoglycoside solution. This nebulises the formulation into an aerosol
5 having a particle size predominantly in the range of 1 to 5 μm . A limited number of nebulisers are suitable for nebulising this formulation. Also, formulations of this kind have quite a large volume, and must be delivered over more than one breath.

The suitable jet-type nebuliser is shown in Figure 3 of WO 96/12471, and consists of a case, a mouthpiece, a nebuliser cup covered with a cap, a venturi chamber, an air supply tube
10 and a baffle. The liquid formulation is placed in the nebuliser cup, and an air supply tube is connected to it. The pressurised air passes from the cup into a jet nebuliser orifice where an aerosol is created by shearing the liquid solution into small threads of liquid that shatter into small particles when they hit the baffle. As a patient inhales through the mouthpiece, air is drawn in through air intake holes in the cap into the venturi chamber where it mixes with the
15 aerosol and is carried to the patient.

All of the nebulisers disclosed are continuously operating nebulisers which generate an aerosol continuously.

In addition, WO 96/12471 mentions a study of the use of nebulisers to determine the pharmacodynamics of aminoglycoside in the sputum of patients which is a measure of the
20 efficacy of the aerosol delivery. Such jet nebulisers were found to be about 10% efficient under clinical conditions, although the amount deposited and absorbed in the lungs is only a fraction of that 10%. Thus, large quantities of the drug must be used if the required dosage of the formulation is to reach the patient. For this reason, the prior art document is directed to a formulation comprising from about 200mg to about 400mg of aminoglycoside dissolved in
25 about 5mls of solution. This is a large mass of drug to be delivered to a patient, and it means that the treatment must be delivered over a number of inhalations lasting maybe several minutes. An example of ten to thirteen minutes to deliver 300mgs is given. Single inhalation atomisers, as disclosed in WO 96/09085 and WO 96/13292, are limited to a maximum drug mass per inhalation of less than 10mgs. Such atomisers are, therefore, not suitable for
30 delivering antibiotics.

Other suitable nebulisers are mesh type nebulisers.

Some drugs, including antibiotics, give no direct feedback to the patient on their effectiveness at the time of inhalation, unlike a bronchodilator for asthmatics which has an

immediate effect in easing the patient's symptoms. Further, the inhalation of aerosols, even when appropriately formulated for pH and tonicity may still cause bronchial constriction and coughing in patients. As a result, the patient has no real idea of how much of the drug has been delivered. He or she merely continues to inhale the atomised substance until there is none left.

In a recent study, the connection between the duty cycle in vitro and the inhaled dose during domiciliary nebuliser use has been investigated. The effectiveness of domiciliary nebuliser therapy is determined by the adherence to a prescribed regimen, the deposition of the drug in the appropriate area of the lungs, and the breathing pattern during nebulisation. The breathing pattern of patients was measured in the laboratory, and from those measurements the patient's duty cycle was calculated. The duty cycle is the proportion of the time the patient spends in inspiration and this normally falls in the range of 0.3 to 0.5. If the patient is inhaling aerosol from a nebuliser, then the amount of aerosol that he or she inhales is directly proportional to his duty cycle. This has been confirmed by measurement of the inhaled dose on a filter during testing, and also using lung scintigraphy.

When similar measurements are made during domiciliary nebuliser use, the duty cycle recorded is significantly less than that recorded in the laboratory. This is because the nebuliser output is continuous and patients interrupt their treatment to rest, talk, drink or as a result of disease related symptoms such as coughing. This reduces the amount of drug inspired by the patient. In addition, using the duty cycle to measure dosage does not take account of whether or not the patient has a good inhalation method, nor whether the patient is adherent to that treatment regimen, for example taking the number of treatments prescribed by their doctor. This makes it particularly difficult to assess why a patient does not respond to the treatment, because the doctor does not know whether it is because the patient is not complying with the regimen prescribed, because the patient is not inhaling properly from the delivery system, or because the drug is ineffective. It is quite clear from various studies that a very high proportion of patients are not adherent to their treatment regimen

Clearly, if the domiciliary duty cycle is much less than the duty cycle measured in a laboratory, the patient is receiving significantly less of the prescribed drug. In addition, a poor inhalation method by the patient and failure to comply with the regimen further reduce the amount of drug received in the lungs of the patient. The percentage of the predicted dose actually received by the lungs of the patient varies enormously. Typically, less than 10% of the initial volume of drug placed in a nebuliser reaches a patient's lungs in domiciliary use.

Thus, it is clear that something of the order of ten times as much of the drug is required to be atomised as actually reaches the patient's lungs.

A number of different types of apparatus for delivering a drug into the lungs of a patient are known. The pneumatic or jet-type nebuliser is particularly effective in supplying an aerosolised drug for inhalation; but other types of nebulisers are available, such as the
5 ultrasonic-type nebuliser in which the drug to be atomised is forced through a mesh by a vibrating piezo-electric crystal whereupon the droplets passing through the mesh are entrained in the air being inhaled by the patient. The mesh gauge determines the size of the droplets which enter the air stream. Alternatively, a dosimetric spacer can be used. When using a
10 spacer, the drug is introduced into the holding chamber of the spacer either in aerosolised form, or by loading the air within the holding chamber with the drug in powdered form. The patient then breathes from the holding chamber, thereby inhaling the drug-laden air. Such spacers are particularly effective when treating children or elderly patients, and for use with certain drugs. The drug is normally delivered over a number of breaths. Of course, the concentration of the
15 drug in each breath decreases over time as a result of dilution caused by ambient air entering the holding chamber to replace air being inhaled by the patient, and as a result of the deposition of the drug within the chamber.

According to a first aspect of the present invention, a drug delivery apparatus comprises a drug delivery device for selectively delivering drug-laden air or air not laden with
20 the drug; a sensor for monitoring the breathing pattern of a patient, a controller arranged to control the drug delivery device to deliver drug-laden air in pulses which begin when the patient is monitored by the sensor to begin inhalation, the pulses having a duration which is adjusted by the controller on the basis of the monitored breathing pattern of the patient; a feedback indicator which indicates to a patient whether the monitored breathing pattern is
25 effective for inhaling drug-laden air or not a dose calculator which calculates the dose delivered to the patient on a breath-by-breath basis; and an indicator which indicates to the patient when a desired dose has been delivered, whereby the apparatus is configured to deliver the full amount of the desired dose in at least 80% of treatments. As a result of these features of the drug delivery apparatus, the desired dosage is delivered in at least 80% of treatments.
30 This is a result of the combination of a number of factors, including the delivery of drug-laden air only in the part of the inhalation phase which reaches the lungs, and also as a result of the patient receiving an indication as to whether or not he or she is inhaling properly. It is also important to indicate to the patient when the appropriate dose has been delivered. The delivery

of the full amount of the dose in at least 90% of treatments, or preferably in at least 90% of treatments is a huge improvement over delivering apparatus which has hereto been used. This improvement offers a number of advantages since almost all of the drug which is delivered is delivered correctly to the correct part of the lungs. This means that considerably less of the drug formulation is required than with existing atomisers. This reduces the cost of the drug, and also shortens the amount of time in which delivery must take place. It may require less than one third of the number of breaths to inhale the correct dose when the apparatus according to the present invention is used over prior art delivery apparatus. In addition, because the apparatus reacts to the patient in order to optimise the length of the pulse in which drug-laden air is delivered, the apparatus is ideal for domiciliary use instead of use merely in hospital. Thus, considerable advantages are received by using the present invention.

It is preferred that the apparatus includes a data log for recordal of information relating to each treatment, including the dose which was delivered. This also adds to the advantages of domiciliary of the apparatus since a doctor can later review the data from the data log to see how well the patient, in fact, complied with the treatments, but in terms of the number of treatments which the patient has taken, and the dose actually received during each of those treatments.

The drug delivery device may be any device which delivers the drug into the lungs of a patient over multiple inhalations. For example, it may be dosimetric spacer including a receptacle defining a holding chamber, a mesh-type atomiser, or a pneumatic-type atomiser.

Other advantageous features are recited in the dependent claims.

The use of such an aerosol delivery system, which only causes atomisation of the drug during inhalation, and adapts to the patient's inhalation pattern significantly reduces the volume of drug required since there is significantly less wastage because no aerosol is generated on exhalation. A particularly surprising effect of the use of such a delivery device is that there is a substantial increase in patients' compliance with the treatment regimen. By compliance, it is meant that patients adhere to the prescribed regimen by actually taking prescribed doses at the right time. It is believed that such a delivery system results in more than 90% of treatments being taken correctly until the device signals that the patient has achieved the correct treatment. Unexpectedly high levels of compliance result from this system, so the present invention gives a significant and unexpected advantage compared with other delivery systems. Whereas only about 10% of the volume of drug placed in a conventional nebuliser reaches a patient's lungs, and it is lower in the case of domiciliary use,

the present invention means that the amount of drug placed in the nebuliser will fall by approximately 50%. This will lead to significant reductions in drug costs, and will also mean that it will take a much shorter time for the required drug to be administered to a patient.

Embodiments of the present invention are described below by way of example, and
5 with reference to the drawings in which:

Figure 1 is a schematic diagram of a dosimetric spacer according to the present invention;

Figure 2 and 3 are schematic diagram showing a second form of dosimetric spacer in which a piston is movable through the holding chamber;

10 Figure 4 is a block diagram of a controller for controlling the operation of the second embodiment shown in Figures 2 and 3;

Figure 5 is a graph showing a breathing pattern of a patient;

Figure 6 and 7 show the upper and lower parts of a nebuliser according to a further embodiment to the present invention;

15 Figure 8 is a flow diagram of the operation of an atomiser of the type shown in Figure 6 and 7;

Figure 9 is a graph showing the predicted tidal volume cluttered against the measured tidal volume; and

Figure 10 shows a two-part drug package for supply of the drug.

20 Referring to Figure 1, a housing 1a defines a holding chamber 1 which includes an inlet 2 through which a liquid or dry powder drug passes into the holding chamber from a source of droplets or particles, for example, a multi-dose inhaler (MDI) 3. The MDI 3 releases the liquid or powder drug in a cloud such that it loads the air with the drug. A sensor 4 is disposed between the MDI 3 and the holding chamber 1 which detects each actuation of the MDI 3. The
25 sensor 4 also detects the rate at which air or other gas enters the holding chamber 1 via the inlet 2.

The holding chamber 1 also includes an outlet 5 to which a mouthpiece 6 is attached. A patient inhales from the mouthpiece 6 drawing air or gas laden with the drug from the holding chamber. This causes ambient air or gas to be drawn into the holding chamber 1 via
30 the inlet 2. The rate of flow of air through the inlet 2 is detected by the sensor 4.

A first valve 7a is disposed between the outlet 5 and the mouthpiece 6 through which drug-laden air passes when the patient inhales. A second valve 7b, is disposed in the mouthpiece 6 which permits exhaled air to be vented to atmosphere. A controller (described in

more detail below in connection with Figure 4) operates to control both the first and second valves (7a, 7b). The first valve must be closed during exhalation so that exhaled air does not enter the holding chamber 1. A second sensor 8 is located in the mouthpiece in order to monitor the breathing pattern of the patient. The controller operates the first and second valves 7a, 7b on the basis of the monitored breathing pattern. When the patient begins to inhale, the second sensor 8 detects this and the controller operates the valves such that the first valve 7a is open and the second valve 7b is closed in order that the patient inhales drug-laden air from the holding chamber 1. Once the controller decides that no more of the drug-laden air is to be delivered to the patient, or the patient stops inhaling, the first valve 7a is closed and the second valve 7b is opened such that the patient finishes any remainder of the inhalation with ambient air which enters the mouthpiece via the second valve 7b, and exhales through the mouthpiece such that the exhaled air is vented to atmosphere via the second valve 7b and does not enter the holding chamber 1. The controller allows inhalation of drug-laden air from the holding chamber 1 in pulses, the duration of which are adjusted according to the monitored breathing pattern of the patient. The controller also analyses the breathing pattern of the patient to ensure that inhalation is suitable for delivering the pulse of drug-laden air. If it is too weak, or too unsteady, the pulse of drug-laden air will not be delivered, or will stop early.

Two indicators 16 and 17 are included in this spacer. The first indicator 16 is a patient feedback indicator which indicates to a patient whether or not suitable inhalation is taking place. In this embodiment, the feedback 16 is a vibrator unit which vibrates gently during inhalation while drug-laden air is delivered. As soon as the first valve 7a closes and the second valve 7b opens, the feedback indicator 16 will turn off. Also, if the patient does not inhale properly, the feedback indicator 16 will either stop vibrating or will not start vibrating. Thus, a patient will quickly learn how to inhale correctly when using the spacer. The feedback indicator could alternatively be an audible indicator emitting, perhaps, a hum while drug-laden air is being delivered, or a visible indicator such as an LED which lights when drug-laden air is delivered.

The second indicator 17 indicates when the patient has received a full dose of the drug, and when treatment has ended. This could be an audible indicator such as a small speaker emitting a tone, or a visual indicator, such as an LED. Of course, if appropriate, the feedback indicator 16 and the second indicator 17 could be combined into a single indicator, preferably a vibrator or a source of an audible signal.

Once the drug has been released into the holding chamber 1, its concentration

decreases, firstly as a result of deposition as the drug settles on the walls and base of the holding chamber due to gravity and electrostatic forces between the housing 1a and the drug, and secondly as a result of dilution caused by air entering the holding chamber via inlet 2 to replace drug-laden air inhaled by the patient.

5 Calculations must be carried out by a dose calculator (not shown) in order to determine the dose of the drug which has actually been delivered to the patient. Details of these calculations are made in our earlier joint patent application published under WO 96/13294, the contents of which are hereby imported into this specification in its entirety. In summary, the dose calculation is carried out on a breath-by-breath basis, the amount of the drug delivered in
10 a breath being added to the amount delivered in each previous breath until the desired dose has been delivered. At that stage, the dose calculator causes the second indicator 17 to indicate that treatment has ended, and the controller no longer allows delivery of the drug-laden air. In addition, the dose calculator includes a formulation input since the spacer can be used for various different drug formulations. The formulation input could be in the form of buttons on
15 the spacer by which the drug formulation being used may be selected. More details of the dose calculator are described in connection with Figure 4.

A further spacer embodiment is shown in Figure 2. This spacer is arranged to operate specifically in conjunction with dry powder inhalers (DPI's). DPI's are normally actuated by the patient's inspiratory flow. They are not suitable for patients with a very low inspiratory
20 flow since the DPI is unlikely to be triggered reliably. DPI's release the drug in the form of a fine powder which is inhaled by a patient into his or her lungs. As with conventional MDI's conventional DPI's suffer from the disadvantage that much of a given dose impacts on the back of a patient's throat. Referring to Figures 2 and 3, a housing 1a defines a holding chamber 1, and includes a first port 9 which is used both to load and empty the holding
25 chamber 1. The spacer also includes a piston 10 movable within the chamber 1. As the piston 10 is drawn back, air or gas is sucked into the holding chamber 1 via the first port 9, and air trapped behind the piston escapes through a second port 11.

In use, and as shown in Figure 2, the piston 10 is pulled back drawing air or gas into the holding chamber 1 through the first port 9. Before reaching the first port 9, the air or gas
30 passes through a dry powder inhaler 13 which releases the drug into the air or gas, and over a sensor 4. The piston 10 is fixed in the retracted position. The patient then removes the DPI 13 and replaces it with a mouthpiece 6 as shown in Figure 3. The patient then inhales via the mouthpiece 6 and the air or gas loaded with the drug is sucked from the holding chamber

passing through the port 9, over the sensor 4 and through the mouthpiece 6. The sensor 4 detects this airflow.

The piston 10 returns across the holding chamber 1 as the patient inhales, and is arranged to move only in the direction of emptying the holding chamber 1 to prevent dilution. To permit the patient to exhale, a one-way valve 14 is disposed in the mouthpiece 6. The mouthpiece 6 also includes a second valve 15 which is controlled by a controller (described below) such that when drug-laden air is not delivered during inhalation of the patient, the valve 15 is opened to allow ambient air to enter the mouthpiece before inhalation by the patient. As will be explained below, this allows the drug to be delivered in pulses. Thus, the controller operates the valve 15 on the basis of information received from the sensor 4 which monitors the breathing pattern of the patient. When it detects a patient inhaling correctly, the controller closes valve 15 so that the patient inhales from the holding chamber 1. Once the pulse of drug for that breath has been received, the valve 15 will open again so that ambient air and not drug-laden air is received by the patient. The duration of the pulse is determined by the controller to optimise the delivery of the drug. During exhalation, the exhaled air is exhausted through the one-way valve 14. It will be noted that, since no ambient air enters the holding chamber during inhalation, any reduction in concentration of the drug within the holding chamber is a result of deposition of the drug within the chamber.

As in Figure 1, two indicators 16 and 17 are present. A patient feedback indicator 16 indicates to a patient whether or not suitable inhalation is taking place, and the second indicator 17 indicates when a patient has received the full dose, and that treatment has ended.

Calculation of the dose given to the patient is now described in connection with the embodiment shown in Figures 2 and 3. The patient firstly connects the DPI 13 to the port 9. The piston 10 is pulled back drawing air into the holding chamber 1 via the DPI 13 and the port 9 so that the holding chamber is charged with the drug. The sensor 4, which might be a microphone or a pressure detector, detects this introduction of the drug into the holding chamber 1 and produces a signal. The dose calculator (not shown) receives the signal from the sensor 4 and starts a clock (not shown). The patient then removes the DPI from the port 9 and replaces it with a mouthpiece (Figure 3). The patient inhales through the mouthpiece, and the air flows past the sensor 4. The dose calculator calculates the amount of the drug delivered to the patient very frequently, typically every one hundredth of a second. The concentration of the drug within the holding chamber 1 is continuously calculated to take account of the deposition of the drug on the walls of the holding chamber 1 over time. A memory contains a

data look-up table which gives the concentration of the drug in the chamber 1 at a time after its introduction. The dose of drug inhaled is then calculated by multiplying the volume of air sensed by the sensor 4 by the concentration of the drug at that time. The dose calculated during this one hundredth of a second sample period is then added to the dose calculated in calculations for previous sample periods. The calculation could, alternatively be calculated on a breath-by-breath basis. Once the cumulative total dose reaches a predetermined level, an indication is made to the patient that the full dose has been given via the second indicator 17.

Figure 4, shows a block diagram of the controller 24 for the spacer shown in Figures 2 and 3, but which would also be suitable for the spacer shown in Figure 1. The controller 24 includes a processor 25 powered by a power supply 34. The sensor 4 sends signals to the processor 25 via an amplifier 32 to indicate when the drug is being introduced into the holding chamber 1, and the rate of inhalation of the patient. The processor 25 calculates the dose given to the patient on the basis of a program 29, a memory 30 containing look-up data 31, and a clock 27. Before treatment starts, it is necessary to enter the drug formulation which is being delivered. One way of doing this is for the apparatus to include a drug formulation input 26 which is in the form of buttons on the apparatus. The apparatus may be suitable for delivering any of a number of drugs to a patient and pressing a button allows the processor 25 to take account of whatever formulation is being used. Information regarding drug formulations is stored in the memory 30. The processor 25 will normally calculate the amount of drug delivered to a patient on a breath-by-breath basis, adding the dose detected to have been delivered in one breath to the amount delivered in each preceding breath. This may be done by sampling the air flow on a regular basis during inhalation. Once the processor has calculated that the predetermined dose has been given, a signal is output to the end indicator 35, and treatment is stopped such that the patient can only inhale ambient air through the mouthpiece, and not medication-laden air.

The processor 25 also analyses the breathing pattern such that, if during inhalation, the patient is breathing correctly, the patient feedback indicator 16 is caused to indicate to the patient that correct inhalation is taking place. Correct inhalation might be considered to take place where the inhalation is above a certain strength, or is of suitable stability. In analysing the breathing pattern, the processor 25 also generates a pulse during which drug delivery takes place. The pulse will not take place, or will be terminated early, if the breathing pattern is not considered to be suitable. Thus, the patient feedback indicator 16 can be caused to indicate to the patient only when correct inhalation is taking place during delivery of the drug. If

inhalation becomes unsuitable for drug delivery during a pulse, the pulse will be terminated early, and the patient feedback indicator 16 will no longer indicate to the patient that correct inhalation is taking place.

In order to deliver the drug in the most effective manner, the processor 25 analyses each breath, and on the basis of the previous breath or breaths, controls the valves so as to deliver the drug in pulses into only a part of the inhalation phase of the patient. The processor includes a pulse generator (not shown) which generates pulses during which the drug is delivered. The pulse generator controls when each pulse begins and its duration. For example, the pulse of drug delivery may occur in the first 50% of the inhalation phase of a patient. However, the duration of the patient's inhalation phase may vary from treatment to treatment, and even during a single treatment. Thus, the processor 25 must adapt to this change. For example, if the processor is generating pulses of drug delivery which correspond to the first 50% of the inhalation phase, it will need to determine the length of the previous breath or a number of the previous breaths using the clock 27.

On the subsequent breath, the pulse length generator of the processor 25 can generate a pulse as soon as it receives a signal from the sensor 4 that the patient has begun to inhale. The length of the pulse will be 50% of the length of the preceding inhalation phase, or 50% of an average of, for example, the preceding three inhalation phases. If the patient fails to inhale correctly, the processor 25 will stop the pulse and indicate to the patient that his or her inhalation is not suitable. The processor 25 controls the valves as described in relation to Figures 1 to 3.

Alternatively, the pulse length may be increased to more than 50%, and a description of a further arrangement in which the pulse length is maximised is described in a later embodiment of this invention. Such an arrangement can be applied to the dosimetric spacer.

The memory 30 can also be utilised to record the dose delivered by the apparatus during each treatment. The processor 25 acts as a dose calculator during each treatment to calculate the dose delivered on a breath-by-breath basis. At the end of a treatment, whether as a result of the full dose being delivered, or as a result of the patient stopping treatment prior to a full dose being delivered, the dose actually delivered is recorded in the memory 30 so that at a later date, a doctor or other person can review the dose received by the patient so as to see whether or not that patient was compliant with the treatments. If, for example, the patient has not responded to treatment, it is possible for a doctor to tell whether or not compliance with the regimen has been adhered to, and if so, a different treatment may be prescribed. Thus, the

memory 30 also constitutes a data log of treatments. It will normally also record the time when each treatment was administered, and might even include information on the patient breathing pattern if required.

Reference has been made above to look up tables which give data on how
5 concentration of the drug decreases in time, and how concentration of the drug decreases by dilution caused by inhalation of known volumes. The data in the look-up tables must be gathered by experiment. For example, when the data for decrease in concentration of the drug with time is gathered, a known amount of the drug is introduced into the holding chamber, and the air in the holding chamber 1 is then expelled after a time into the filter paper. The expelled
10 drug is then weighed. This experiment is repeated for different time periods to establish the necessary data. The variation of concentration with time profile is likely to be different for different drugs. Therefore the apparatus must have the correct profile programmed in.

A nebuliser according to the present invention will now be described. In order to appreciate the invention, reference is made to Figure 5 in which the inhalation pattern of a
15 patient is shown over time. It will be appreciated that breathing patterns are not very regular, and that some breaths are deeper than others.

Figures 6 and 7 of this application show a nebuliser. Referring to Figure 6, a mouthpiece 101 is shown through which a patient inhales in the direction of arrow 102. Below the mouthpiece 101 is a removable atomising section 103 which, in turn, rests on a base 104.

20 The base 104 is shown in more detail in Figure 7. Referring to Figure 7, the base 104 includes an inlet 105 through which air is supplied under pressure from a compressor (not shown). The pressurized air is led via a tube 106 to a manifold 107 which controls the flow of pressurized air to an air outlet 108 which directs air into the atomising section 103 shown in Figure 6. The base 104 also includes a pressure sensor 109 which detects the pressure within
25 the atomising section 103 via a port 110.

Referring again to Figure 6, air under pressure passes through the air outlet 108 of the base 104 and is conducted through a tubular post 111 to an atomiser nozzle 112 out of which the air issues under pressure. A deflector 113 is located in the path of the pressurised air issuing from the nozzle 112 so that the pressurized air is deflected laterally so as to pass
30 beneath a baffle 114. The passage of the pressurized air across the top of the tubular post 111 causes a drug 115 to be drawn up between the outer surface of the tubular post 111 and the inner surface of a sleeve 116 which surrounds the tubular post 111. The drug 115 is atomised in the stream of air, and carried away in the stream of air below the rim of the baffle 114 and

up through the mouthpiece 101 to a patient.

The pressure sensor 109 in the base 104 monitors the breathing pattern of a patient, and on the basis of the breathing pattern, the manifold 107 is controlled to supply pressurized air to the atomising section 103 in pulses only during the first 50% of an inhalation phase so that
5 drug delivery only occurs during that pulse.

This invention applies to atomisers which generate drug delivery pulses. The invention is not, however, limited to the exact atomiser described above, but may be applied to other atomisers. For convenience, the description below of the present invention will refer to components of the device shown in Figures 6 and 7, but it can be applied to other atomisers,
10 such as other designs of jet nebulisers, ultrasonic atomisers and pressure mesh atomisers.

Jet nebulisers are of two kinds, these being air-jet nebulisers and liquid-jet nebulisers. An example of an air-jet nebuliser, which uses a source of compressed air to nebulise a liquid, is disclosed in EP 0627266 (Medic-Aid Limited), the content of which is incorporated herein in its entirety by reference. An example of a liquid-jet nebuliser, which drives a liquid through
15 one or more nozzle outlets to produce a spray of fine droplets is disclosed in WO 94/07607 (Boehringer Ingelheim International GmbH et al), the content of which is incorporated herein in its entirety by reference.

Ultrasonic nebulisers nebulise a liquid drug using ultrasonic waves usually generated with an oscillating piezo-electric element and take many forms. These include nebulisers 1) where liquid is in direct contact with the piezo-electric element, 2) where there is an
20 amplifying interface, typically an enclosed fluid, between the piezo-electric element and the liquid, and 3) where the piezo-electric element vibrates a mesh from which an aerosol is generated. Examples of ultrasonic nebulisers are disclosed in US 4533082 (Maehara et al) and US 5261601 (Ross et al), the contents of which are incorporated herein by reference. The
25 nebulisers described in those documents include a housing that has a reservoir which holds a quantity of liquid to be dispensed, which housing has a perforated membrane in contact with the reservoir and an ultrasonic vibrator connected to the housing to vibrate the perforated membrane. Another example of an ultrasonic nebuliser is described in WO 97/29851 (Fluid Propulsion Technologies, Inc), the contents of which are incorporated herein by reference. An
30 example of a pressure mesh nebuliser, which may or may not include a piezo-electric element, is disclosed in WO 96/13292 (Aradigm Corporation), the contents of which are also incorporated herein by reference.

As mentioned above, all of the above types of nebuliser can be used to atomise the drug

in pulses. This means that atomisation and drug delivery can be switched on and off. The pulses can be controlled so that atomisation only occurs during a part of the breathing pattern of a patient in which it will be of benefit. With reference to the device shown in Figures 6 and 7, the sensor 109 is extremely important in that this measures the breathing pattern of the patient. A controller (not shown) receives the breathing pattern information from the sensor 109 and analyses the breathing pattern of the patient. It will calculate the length of time in which the patient inhales, and on the basis of that information will control the manifold 107 such that atomisation only occurs in a pulse of drug delivery during a part of the inhalation of the patient.

The controller may be of the same form as that disclosed in Figure 4. In that arrangement, the controller includes a processor 25 which carries out a number of functions, acting as generator of pulses of drug delivery, a dose calculator for calculating the dose delivered on a breath-by-breath basis, and a breathing pattern analyser for analysing the breathing pattern of a patient and, determining whether or not the patient is breathing correctly so that a feedback indicator can be used to indicate to the patient whether or not correct inhalation is taking place. In addition, the processor can take account of different formulations provided that the apparatus includes an input for entering the drug formulation being used. The controller can also log information concerning the treatments, such as the dose delivered, when each treatment was delivered, and information on the breathing pattern of the patient.

For example, a good arrangement is to generate a pulse of drug delivery only in the first 50% of the inhalation of the patient. Since the duration of inhalation of a patient varies between treatments, and also within a single treatment, it is necessary to monitor the duration of inhalation over one or more breaths so that the average duration of inhalation can be calculated in order that the pulse length can be determined for the next breath. Once determined by the controller, as soon as the controller receives an indication from the sensor 109 that inhalation has started, it will generate a pulse of drug delivery equal to half of the average duration of inhalation of the patient. In addition, the inhalation of the patient is analysed to ensure that it is suitable for delivering the drug. If the breath is too weak or is interrupted, or is very uneven in strength, the pulse of drug delivery will not begin, or will be terminated early. To assist the patient in knowing what is a suitable breath and what is not, the nebuliser includes a patient feedback indicator (not shown) which indicates to the patient either that the breath is suitable, or that it is unsuitable. This may be a visual or audible indicator, or even a small vibrator. It is preferred that the nebuliser indicates when a patient is inhaling

correctly, and the signal received by the patient could coincide with the pulse of atomisation. In this way, if the inhalation is not suitable, the pulse of atomisation is stopped, and the indication that the patient is inhaling correctly will also be stopped.

An end indicator (not shown) is also included which indicates to the patient when the full dose has been dispensed. To do this, the atomiser also includes a dose calculator which calculates the amount of the drug received by the patient on a breath-by-breath basis. The output of the device will be known through experimentation so that the total length of the pulses can be multiplied by the output rate of the nebuliser to give the total dose received by the patient. Once the dose calculator has determined that the full dose has been delivered, the end indicator indicates to the patient either audibly or visibly that treatment has ended. The controller will not then generate any further pulses for that treatment.

Extending the proportion of the inhalation of the patient in which atomisation takes place above 50% results in the patient receiving their treatment faster since it will take fewer breaths to deliver the required volume of medication. However, to avoid wastage of the medication which is atomised in the end volume of patient's inspiratory volume, the pulse of atomisation must be stopped before the end volume is reached. The end volume is the volume of air inhaled by a patient at the end of the inspiratory volume which remains in the upper airways (the mouth and trachea) and does not enter into the lower parts of the lungs. Any drug which is atomised into the end volume is wasted when the patient exhales, together with any atomised drug left in the nebuliser, since it does not reach the lungs.

The end volume is the volume of the patient's upper airway, and is proportional to the size of the patient. Clearly, the end volume will vary as a percentage of the inspiratory tidal volume since the tidal volume changes significantly depending on the type and extent of the respiratory disease suffered by the patient. The optimum duration of an atomisation pulse would, therefore, be from the start of inhalation up to the point during inspiration when the volume remaining to be inspired equals the end volume. Atomisation would then be stopped and the remaining end volume would clear the atomised medication from the device and the upper airways of the patient and into the lungs. Thus, the percentage of inspiration in which atomised medication is delivered is maximised, thereby minimising treatment time and still avoiding wastage of medication. The length of the atomisation pulse is dependent upon the patient's inspiratory tidal volume. The nebuliser must therefore measure the patient's tidal volume, preferably on a breath by breath basis so as to calculate, for example from the previous three breaths, an average inhalation volume for the next breath. Thus, the atomisation

pulse time will be calculated as follows:

$$\text{Pulse time} = \text{mean inspiratory time} \times \frac{(\text{mean tidal volume} - \text{end volume})}{\text{mean tidal volume}}$$

5

A timer is included in the nebuliser connected to the pressure sensor 109 (shown in Figure 7) in order to measure the duration of inspiration. Storage means are also included in the nebuliser in which an estimate of the end volume of a particular patient is stored. Since this figure is a constant value for a particular patient, this can be entered at the beginning of a course of treatment, and is estimated on the basis of the size of the patient. The nebuliser includes a means for measuring the tidal volume of a patient. According to one form of the invention, the patient's inspiratory flow is monitored continuously, typically every ten milliseconds, and this is integrated over the inspiratory duration. Another, simpler, way of measuring the tidal volume of a patient is described later in this specification.

15

The nebuliser also includes means for calculating the atomisation pulse time on the basis of the duration of inspiration, the tidal volume and the end volume. The calculation means carries out the calculation outlined above.

In view of the fact that the nebuliser adapts to the breathing pattern of a patient, when the patient starts breathing, no atomisation takes place during the first three breaths. Those first three breaths are used to analyse the breathing pattern of the patient. The flow rate of the first three breaths are measured, and from this, the duration of the inhalation phase of the first three breaths are calculated, and an average found. The average duration of inhalation is then used in the calculation to determine the pulse length of atomisation during the fourth breath. In addition, as the patient continues to breathe in and out, the previous three breathing patterns are measured and used to calculate the next pulse duration. Thus, if a patient's breathing pattern improves during treatment, the nebuliser will adapt to this change in order to optimise the dose administered during each breath.

Referring now to Figure 8, the steps taken by the nebuliser, and by the patient are described. The first operation, box 130 represents the patient starting to inhale. The timer records the time at which inhalation starts as shown in box 131, and during inhalation, a calculation is performed to predict the tidal volume of the patient as shown in box 133. This step will be described in more detail later in a specification, but it will be noted that the calculation requires data to be included in the calculation including the inhalation time and peak flow as an average from the last three breaths, as shown in box 132. The pulse time is

then calculated as shown in box 134, and the pulse time is adjusted, as shown in box 135 in the event that the pulse length would exhaust an accumulator from which is pressurised air is supplied to the nebuliser. The pulse of atomisation occurs during inhalation, and after it has stopped, a calculation is carried out to determine what dose has been atomised. At the end of
 5 the breath as shown in box 138, details of the peak flow of the patient inhalation, and the duration of inhalation are recorded so that calculations determining pulse length may be made for subsequent breaths. This is shown in box 139.

Reference is made above to the simpler prediction of tidal volume. As will be appreciated, measuring tidal volume by integrating measured flow rate over the time of
 10 inspiration requires considerable processing power and is relatively expensive. A simpler method of determining the tidal volume is proposed which requires much simpler calculations and much simpler measurements to be made for use in such a calculation. To carry out the measurement, the nebuliser includes a peak flow detector for detecting the peak flow rate of inspiration.

15 The calculated, or predicted tidal volume is derived from the peak flow measured by the peak flow detector, and the duration of inspiration measured by the timer. The tidal volume calculation means carries out the following calculation:

$$20 \quad \text{Predicted tidal volume} = C \times \text{Mean Peak Flow} \times \frac{\text{Inspiratory Time}}{60}$$

C is a constant and it is found that $C = 0.7$

Figure 9 is a graph of the predicted tidal volume against measured tidal volume. Each point on the graph represents a patient whose tidal volume has been measured by a complex
 25 tidal volume calculation by integration of the patient's inspiratory flow over the duration of inhalation, and the predicted tidal volume according to the new, simpler method of calculation. It will be seen that the predicted tidal volumes are extremely accurate, and so the predicted tidal volume may be included in the calculation of atomisation pulse time.

The use of this invention provides a particularly effective therapy when multiple
 30 inhalations are required, as is usually the case for systemic drug delivery via the lung alveoli or local drug delivery to the lung for respiratory disease, as in the case of the use of anti-infective drugs. It significantly reduces the volume of drug required because there is reduced wastage as no aerosol is generated on exhalation and lost to the environment, but only on the initial phase of inhalation. Also, such an atomiser informs the patient when treatment is complete and the

correct dose is received. This prevents the patient from receiving too much of the medication or an overdose, and ensures that enough of the drug is received for proper therapeutic effect. With antibiotic drugs, for example, where such large quantities are required to be administered, it has been unexpectedly found in tests that there is a significant increase in a patient's compliance with the treatment regimen, at least to 80% of treatments and normally to at least 90% of treatments.

Figure 10 shows a drug package suitable for storage of most aerosol drug products, including anti-infectives and proteinaceous material, and their administration into the drug delivery apparatus. Many aerosol drug products, when in solution, have a limited stability and shelf-life. Consequently, such products, as stated herein, are supplied in a dried form, such as a powder, crystalline, micronized or lyophilized solid material, which must be reconstituted prior to inhalation. Other aerosol drug products in their final liquid formulation may have a limited shelf-life as well. Consequently, such products require their ingredients to be admixed at the time of inhalation. Figure 10 shows an example of a drug package suitable for supplying aerosol drug products that require packaging in a dried form or require their liquid ingredients to be separated until use. Those skilled in the art will appreciate that Figure 10 shows a drug package that can integrate with a drug delivery device to enable the proper and accurate administration of a reconstituted dried aerosol solution or even an aerosol drug packaged therein as two separate liquid components. The package includes a body 201 from which extends a tube 202. From the opposite side of the body 201 extends a piston 203, which may be pushed through the body 201 and into the tube 202. For this reason, the piston 203 includes a knob 204 so that the fingers of a person can push the piston 203 inwardly by squeezing the knob and a flange of the body 201 together.

The tube 202 is divided into a first chamber 205 and a second chamber 206 separated by a stopper 207. The end of the tube 202 furthest from the body 201 is closed by a closure 208. The end of the tube 202 is designed to integrate with the drug delivery apparatus at either the mouthpiece, baffle, medication chamber, or other suitable location so as to provide a direct connection for the liquid or reconstituted aerosol drug product to enter the drug delivery apparatus. The first chamber 205 contains the solid drug product and the second chamber 206 contains a diluent/solvent in which the dry/dried product is soluble. Alternatively, the first chamber 205 contains a liquid constituent of drug product and the second chamber 206 contains the other miscible liquid constituent. The stopper (207) keeps the two apart until mixing is required.

The piston 203 is threaded towards the end closest to the body 201 and the body 201 includes internal threads which engage with the threads 209 of the piston 203.

In use the piston 203 is turned with respect to the body 201 so that the piston pushes the material from the second chamber 206 past the stopper 207 into the first chamber 205 where
5 mixing of either the solid and liquid or liquid and liquid components of the aerosol drug product takes place. The piston is then pushed through the body 201 such that the liquid drug product is expelled from the tube 202 at the end which contains the closure and attachment (integration) with the drug delivery apparatus or atomizer. The liquid aerosol product is thus expelled directly and accurately into the atomizer.

10 It can also be appreciated by one skilled in the art that the drug package suitable for storage of most aerosol drug products and their expulsion into the atomizer, may be designed with only a single chamber, where the first chamber 205 and second chamber 206 are not separated by a stopper 207. This one part drug package would be suitable for use with liquid aerosol drug products that can be packaged in their final formulation, i.e., the formulation that
15 is inhaled and dispensed directly and accurately into the atomizer.

In order to describe the advantageous effect of the apparatus, examples of the drugs which may be used will now be described. The drugs concerned require treatment over multiple breaths due to the volume of drug delivered. Solution based formulations require between 0.1 and 0.5 ml to be delivered, and powder-based drugs between 1 and 5 mgs. Most
20 of such drugs are used for prophylactic treatment and do not give any direct feedback in terms of benefit at the time of treatment nor negative feedback such as coughing.

In the following, it should be understood that the "lung dose" is the amount of a drug which reaches the lungs, and that to achieve the lung dose, it is necessary to deliver more than that since some of the drug will not reach the lungs.

25 An important drug which is delivered to the lungs is Tobramycin. A typical treatment of Tobramycin requires the delivery of 30 mgs to the lungs. A typical nebuliser delivers about 10% to the lungs which means that 300 mgs of Tobramycin must be nebulised. 300 mgs would normally be dissolved in 5 mls of 0.225 % NaCl having a pH of 5.5 to 6.5. Thus, the concentration is 60mg/ml. However, the use of the present invention allows considerably less
30 of the drug to be used. Since delivery efficiency is at least 80%, if a dose of 15 mgs is required to reach the lungs, only 19 mgs needs to be delivered. The formulation can be the same as is described above in connection with existing nebulisers, but the amount of the drug used is much less. Of course, in addition to the amount of the drug which is dispensed, a delivery

apparatus will have a dead volume which is residual and remains in the delivery device even if delivery continues. For example, with some pneumatic or jet-type nebulisers, the dead volume may be as much as 0.8 ml. However, a mesh-type atomiser could have a dead volume of at little as 0.1 ml. Thus, the amount of the drug which is actually placed in the drug delivery device may be 1.01 mls for the jet-type nebuliser (0.8ml dead volume + 0.21 ml for delivery),
5 or 0.42 ml for the mesh-type atomiser (0.1ml dead volume + 0.32ml for delivery). Of course, other types of drug delivery device will have different dead volumes, and so the actual amount of the drug supplied for those devices will be different.

To provide effective control of one of the main infective lung organisms "Pseudomonas aeruginosa" in cystic fibrosis patients the concentration of Tobramycin in the lung fluid must
10 exceed the minimal inhibitory concentration (MIC) for the organism to be eliminated. For Tobramycin the MIC level is typically required to be $>16\mu\text{g/ml}$ for 90% of organisms, and the MIC concentration should be maintained at this level for 120 minutes.

To compare the performance of a conventional nebulizer and a high compliance system according to this invention using Tobramycin 8 patients received either 300mg/5ml via
15 conventional nebulizer or 30mg delivered dose via the high compliance system. The mean sputum tobramycin concentrations at 2 hours were $128\mu\text{g/g}$ for the conventional nebulizer and $98\mu\text{g/g}$ for the high compliance system. This study may indicate that an even lower dose may be acceptable to achieve the MIC level when delivered with a high compliance system such as
20 disclosed in this invention, in the range 5-30mg Tobramycin.

Tobramycin is a stable drug and can be packaged as a unit dose solution in a one-part package as described above in connection with a modified Figure 10 or in a single glass or plastic unit dose vial.

If the drug Colistin is used (colistin sulphomethate) then the maximum daily dose is 6
25 million units in three treatments. This is an equivalent lung dose of 600,000 U per day, but with the present invention delivering 300,000 U per day at an efficiency of over 80% allows only 375,000 U to be delivered by the atomiser per day over two treatments of 187,000 U per treatment. Thus, a very significant reduction in the amount of the drug is achieved. Four examples of the drug formulation for Colistin are described below. In the first formulation, one
30 million units of Colistin is dissolved in two mls of 0.9% NaCl. In the second, the Colistin is dissolved in a two mls solution made up from 0.75 ml of 0.9% NaCl and 1.275 ml of water.

Alternatively, the formulation can include an additional bronchial dilator such that the Colistin is dissolved with 2.5 mgs of salbutamol in 2.5 mls of 0.9% NaCl, or alternatively with

2.5 mgs of salbutamol dissolved in 0.75 mls of 0.9% NaCl plus 1.275 mls of water. Finally, the Colistin can be dissolved in a solution including 2.5 mg of DNase in 2.5mls of 0.9% NaCl. Since Colistin is not stable in solution, it is supplied as a powder which must be pre-mixed with a dilutant either supplied in a different vial, or in a two-part package, as described above in connection with Figure 10. In the present application, the actual volume of the Colistin formulation required to be placed in the drug delivery apparatus may be 0.48 ml for a mesh atomiser, or 1.18 mls for a jet nebuliser, much less than in conventional nebulisers. Of course, other drug delivery apparatus will require different volumes according to their dead volume.

Another drug which can be delivered in the same way with similar advantages is DNase. The required lung dose in a normal nebuliser is 0.25 mgs. 2.5 mgs of DNase in 2.5 mls 0.9% NaCl is required in normal (conventional) nebulisers. However, in the present invention a lung dose of 0.125 mg delivered with 80% efficiency requires a dose of only 0.156 mg, much less than in conventional nebulisers. The high efficiency is the result of a particle size of the drug being within a narrow range of sizes, about 3 microns in diameter. That way, 80 % of the delivered drug reaches the lungs and stays there. Only 20% loss occurs due to impaction and exhalation.

Depending on the dead volume, the amount of drug supplied for a jet nebuliser may be 1.06 mls, and for a mesh atomiser 0.26 ml. Other drug delivery apparatus will require different volumes depending on their dead volume.

Approximately 38% of patients show a greater than 10% change in FEV₁ over baseline when starting rhDNase therapy. Some patients may not respond to inhaled therapies due to poor nebulizer techniques such as nose breathing, talking, coughing, resulting in poor inhalation compliance.

A study to assesses the response to rhDNase delivered by a system according to this invention in patients who have previously failed to respond to therapy with conventional nebulizer devices.

Eight Adult CF patients who had previously failed to respond to rhDNase therapy (mean response to therapy 4.17% change in FEV₁) used aerosolized rhDNase delivered for 10 days using 0.25ml/0.25mg of the formulation. the device. Mean change in FEV₁ was 11.51%.

This result shows that in CF patients who have previously failed to respond to inhaled therapies, have an improved response with a high compliance delivery system, compared to their conventional nebulizer. This study may indicate that an even lower dose may be acceptable when delivered with a high compliance system such as disclosed in this invention,

in the range 0.06/0.25mg rhDNase.

A further suitable drug is A1AT (Alpha 1 Antitrypsin) for which the lung dose for a conventional nebuliser is typically 20 mgs requiring nebulisation of some 200mg of the drug in 4ml of 0.9% NaCl. Because of the delivery efficiency of the delivery device according to the present invention, a lung dose of 10 mgs is required with the nebuliser delivering 12.5 mgs of the formulation having a concentration of 50 mg per ml of 0.9% NaCl. In our jet-type nebuliser, the volume of drug required will be 1.05, but in a mesh type atomiser will be 0.35 ml. Other drug delivery apparatus will require different volumes according to their dead volumes.

A1AT is supplied as a powder requiring dilution with water. A two-part package such as is disclosed in Figure 10 will be suitable for a supply of the drug dilutant.

Another drug is cyclosporine which is normally delivered by a nebuliser requiring a lung dose of 100 mgs at a concentration of 125 mgs per ml. Normally, 500 mg of cyclosporine in 4 ml of propylene glycol must be nebulised. A lung dose from the present invention is 50 mgs using only 62 mgs of the same formulation.

The amounts supplied for a typical jet nebuliser will be 1.3 mls, and for a mesh type atomiser 0.6 ml. Other drug delivery apparatus will require a different volume depending on its dead volume.

Budesonide is a corticosteroide with a high topical anti-inflammatory activity, it is important in the management of asthma. To be effective steroids must be delivered over long periods ranging from months to years. However it is important to minimise the dose delivered as there can be significant side effects on the adrenal function, calcium metabolism and growth rate in children. There are also local side effects including irritation in the throat, candidiosis, and dysphonia.

Budesonide for nebulisation is typically formulated as 1000 mg, 500 mg or 250 mg in 2 ml for conventional nebulizers.

A study in 125 children with asthma using the system disclosed in this patent delivered three different regimes of a short duration (2-12 weeks) high delivered daily dose 200µg followed by a long duration (12-22 weeks) low daily dose delivered dose 50µg. Their treatment compliance was monitored electronically and their asthma symptoms by the parents using a visual analogue score. The treatment compliance over the study was 80/90% and the asthma scores reduced from a baseline of 1.23/1.27 to 0.23/0.43.

The study in 481 children with asthma using conventional nebulizers delivered five

different regimes. Nominal nebulizer doses were in the range 250/1000µg daily and placebo over a 12 week period. Their asthma symptoms by the parents using a visual analogue scores, the asthma scores reduced from 1.21/1.33 to 0.87/0.93.

The comparative data in table 1 shows that the system according to this invention improved asthma scores by approximately twice as much as the conventional nebulizer using a low long-term daily dose. This study may indicate that an even lower daily dose may be acceptable when delivered with a high compliance system such as disclosed in this invention, in the range 12-50µg budesonide. When delivered from a formulation of 500µg/ml would required only 0.024/0.1 ml of formulation.

This invention can also be applied to other corticosteroides such as Fluticasone currently delivered by conventional nebulizer in a formulation of 250µg/2000µg in 2.5ml . A delivered daily dose in the range 6-50µg may be required, from an 800µg/ml formulation would require 0.0075/0.063ml.

Table 1 Budesonide Nebulising Suspension

Study results daytime asthma symptom scores (Visual analogue range 0-3 where 0 is no symptoms)

	Conventional Nebuliser					Improved Invention System		
	Placebo	250µg Once daily	250µg Twice daily	500µg Twice daily	1000µg Once daily	200/50µg 2/22 weeks	200/50µg 6/18 weeks	200/50µg 12/12 weeks
Baseline at entry	1.27	1.21	1.31	1.33	1.28	1.23	1.26	1.27
End of Study	1.08	0.93	0.91	0.87	0.91	0.23	0.43	0.36
Change	0.19	-0.28	-0.4	-0.46	-0.37	-1	-0.83	-0.91

Other drugs suitable for use are antiviral/antiinfective drugs Gamma Interferon (IFN*), Synagis™, Virazole® and SuperVent™, antifungal drugs such as AmBiosome®, corticosteroids such as Budesonide®, Surfactant drugs Exosurf® and Surfaxin™. Other drugs suitable for use are hormones, including growth hormone, Erythropoitin, Parathyroid Hormone, Lureinizing Hormone Releasing Hormone (LHRH). Also drugs for pulmonary hypertension (PPH) including Iloprost, Flolan and UT15, and for pain control opiates and cannabinoids including Dronabinol (THC), Morphine and Marinol®.

Other drugs suitable are insulin for diabetics and Calcitonin for osteoporosis.

CLAIMS

1. Drug delivery apparatus comprising:
 - a drug delivery device for selectively delivering drug-laden air or air not laden with the drug;
 - a sensor for monitoring the breathing pattern of a patient
 - 5 a controller arranged to control the drug delivery device to deliver drug-laden air in pulses which begin when the patient is monitored by the sensor to begin inhalation, the pulses having a duration which is adjusted by the controller on the basis of the monitored breathing pattern of the patient;
 - a feedback indicator which indicates to a patient whether the monitored breathing
 - 10 pattern is effective for inhaling drug-laden air or not
 - a dose calculator which calculates the dose delivered to the patient; and
 - an indicator which indicates to the patient when a desired dose has been delivered, whereby the apparatus is configured to deliver the full amount of the desired dose in at least 80% of treatments.
- 15 2. An apparatus according to claim 1, configured to deliver the full amount of the desired dose in at least 90% of treatments.
3. An apparatus according to claim 1 or 2, wherein the dose calculator includes a
- 20 formulation input through which the formulation of the drug being delivered is entered for use in the calculations made by the dose calculator.
4. An apparatus according to any one of the preceding claims, further comprising a data log for recordal of information relating to each treatment, including the dose which was
- 25 delivered.
5. An apparatus according to any one of the preceding claims, wherein the controller includes a pulse length generator which determines the duration of each pulse on the basis of the monitored breathing pattern of the patient.
- 30 6. An apparatus according to claim 5, wherein the pulse length generator includes a

breathing pattern analyser which analyses the breathing pattern of a patient in order to determine the time at which a patient begins to inhale an end volume, the end volume being the volume of the upper airways of the a patient which, at the end of the inhalation, contains the end volume of air which does not reach the lungs.

5

7. An apparatus according to claim 6, wherein the pulse length generator generates a pulse having a length which stops delivery of drug-laden air into the end volume.

8. An apparatus according to claim 6 or 7, wherein the breathing pattern analyser includes
10 a tidal volume measuring device for measuring the tidal volume of a patient, a timer for measuring the duration of inhalation of the patient, and an estimate storage device for storing an estimate of the volume of the patient's upper airways, and an end volume estimator which determines the time at which the patient begins to inhale the end volume on the basis of the measured tidal volume, the measured duration of inspiration, and the stored estimate of the
15 volume of the patient's upper airways.

9. An apparatus according to claim 8, wherein the analyser further includes an averaging device whereby the time at which the patient begins to inhale the end volume is determined on the basis of an average of the values collected by the analyser over more than one breath.

20

10. An apparatus according to any one of the preceding claims, wherein the sensor is a pressure sensor.

11. An apparatus according to any one of the preceding claims, wherein the feedback
25 indicator is a vibrator which causes the apparatus to vibrate in order to indicate that the patient is inhaling effectively.

12. An apparatus according to any one of the preceding claims 1 to 11, wherein the drug
30 delivery device is a spacer including a receptacle defining a holding chamber in which the air within the holding chamber is loaded with the drug prior to treatment.

13. An apparatus according to any one of claims 1 to 11, wherein the drug delivery device is an atomiser which atomises the drug during inhalation into a stream of air leading to the

patient.

14. An apparatus according to claim 13, wherein the drug delivery device is a mesh-type atomiser.

15. An apparatus according to claim 13, wherein the drug delivery device is a pneumatic atomiser in which atomisation of the drug is caused by pressurised air.

16. In a drug delivery apparatus according to any one of claims 1 to 15, the use of a drug formulation in which about 19 mg tobramycin is dissolved in a solvent.

17. The use of the drug formulation according to claim 16, wherein the solvent is about 0.3 ml in volume.

18. The use of the drug formulation according to claim 16 or 17, wherein the drug formulation further comprises an additional amount of between about 6 and 50 mg tobramycin in about 0.1 to 0.8 ml solution which fills the dead volume of the delivery apparatus and which is residual once all of the drug which can be delivered has been delivered.

19. The use of the drug formulation of any one of claims 16 or 18, wherein the concentration of tobramycin is about 60 mg/ml.

20. In a drug delivery apparatus according to any one of claims 1 to 15, the use of a drug formulation including about 187,000 U colistin.

21. The use of a drug formulation of claim 20, in which the colistin is in a concentration of about 1 million units/2 ml in one of the following solutions:

a) 2 ml 0.9% NaCl

b) a 2 ml solvent including 0.75 ml 0.9% NaCl and 1.275 ml water

c) a solution of 2.5 mg salbutamol in 2.5 ml 0.9% NaCl

d) a solution of 2.5 mg salbutamol in 0.75% 0.9% NaCl and 1.275 ml water

e) a solution of 2.5 mg DNase in 2.5 ml 0.9% NaCl, or

f) a solution of 2.5 mg DNase and 2.5 mg sulbutamol in 2.5 ml 0.9% NaCl.

22. The use of the drug formulation of claim 20 or 21, wherein the drug formulation further comprises an additional amount of between about 0.1 to 0.8 ml of the formulation which fills the dead volume of the delivery apparatus and which is residual once all of the drug which can
5 be delivered has been delivered.
23. In a drug delivery apparatus according to any one of claims 1 to 15, the use of a drug formulation including about 0.156 mg DNase in a solvent.
- 10 24. The use of a drug formulation according to claim 23, wherein the solvent has a volume of about 0.156 ml.
25. The use of a drug formulation according to claim 23 or 24, wherein the drug formulation further comprises an additional amount of between about 0.1 to 0.8 ml of the drug
15 formulation which fills the dead volume of the delivery apparatus and which is residual once all of the drug which can be delivered has been delivered.
26. In a drug delivery apparatus according to any one of claims 1 to 15, the use of the drug formulation including about 12.5 mg AIAT in solvent.
- 20 27. The use of a drug formulation according to claim 26, wherein the solvent has a volume of about 0.25 ml.
28. The use of a drug formulation according to claim 26 or 27, wherein the drug
25 formulation further includes an additional amount of between 0.1 ml and 0.8 ml of solvent.
29. In a drug delivery apparatus according to any one of claims 1 to 15, the use of a drug formulation including about 25 μ g of Budesonide in a solvent.
- 30 30. The use of a drug formulation according to claim 29, wherein the volume of the solvent is about 0.05 ml.
31. The use of a drug delivery apparatus according to any one of claims 1 to 15, the use of

a drug formulation including about 12 μ g of fluticasone.

32. A drug product comprising a drug formulation according to any one of claims 16 to 25, and a multi-part package within which the formulation components are mixed prior to delivery.

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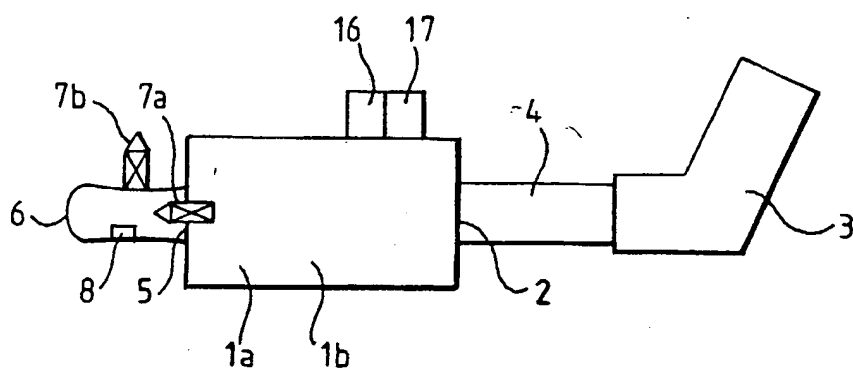


Fig.1.

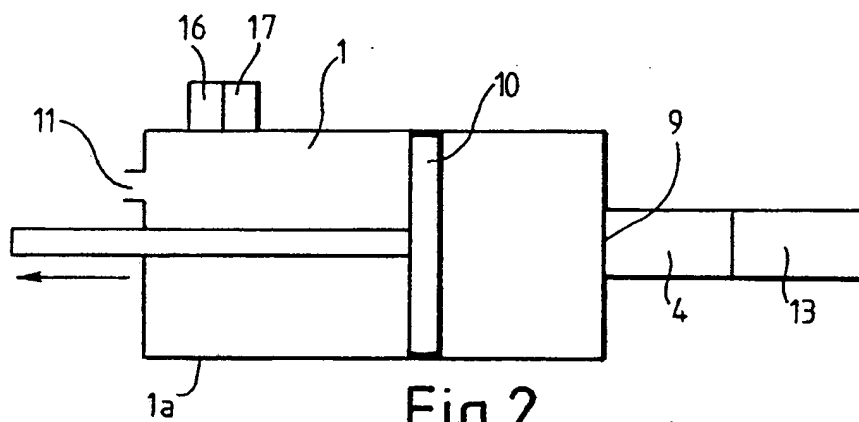


Fig.2.

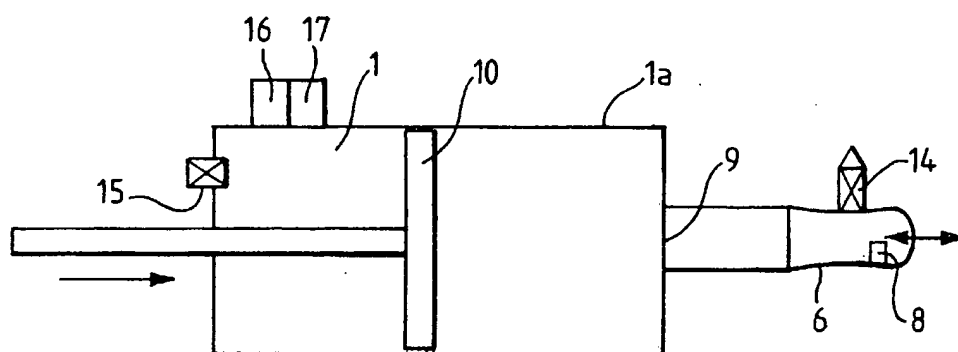


Fig.3.

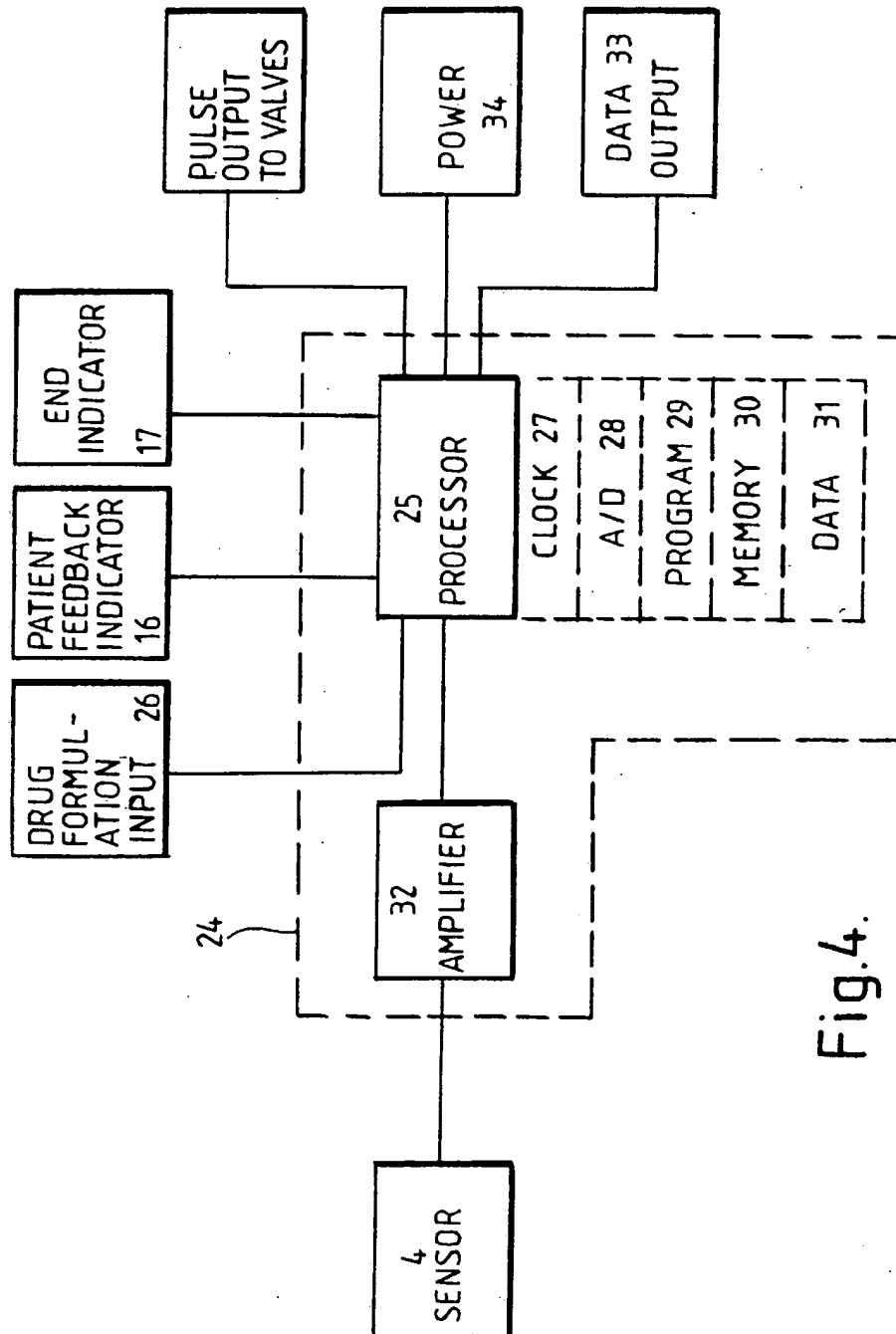
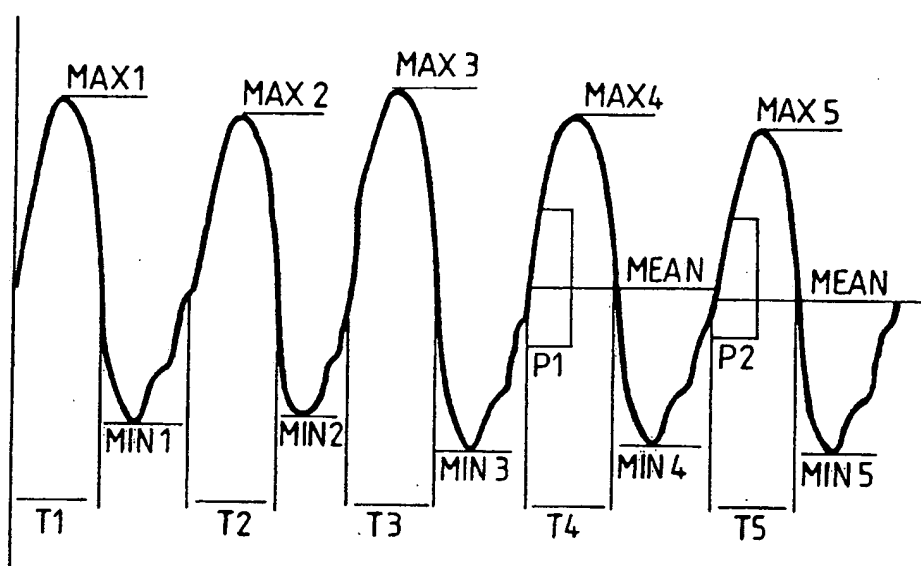


Fig. 4.

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$$\text{Pulse time} = 50\% \sum \frac{(T1 + T2 + T3)}{3}$$

$$\text{Dose} = \text{Sum } (P1 + P2 + \dots)$$

Fig.5.

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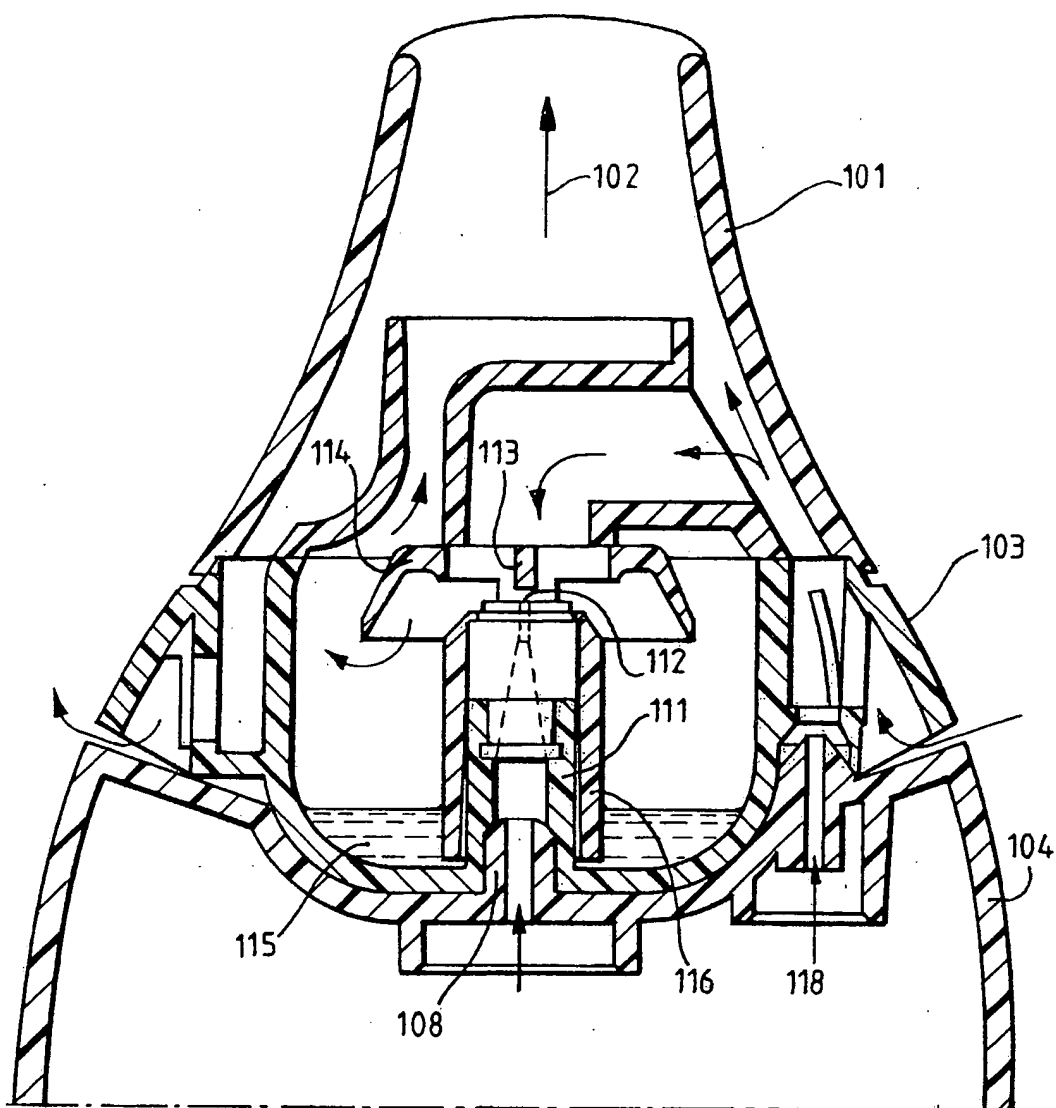


Fig.6.

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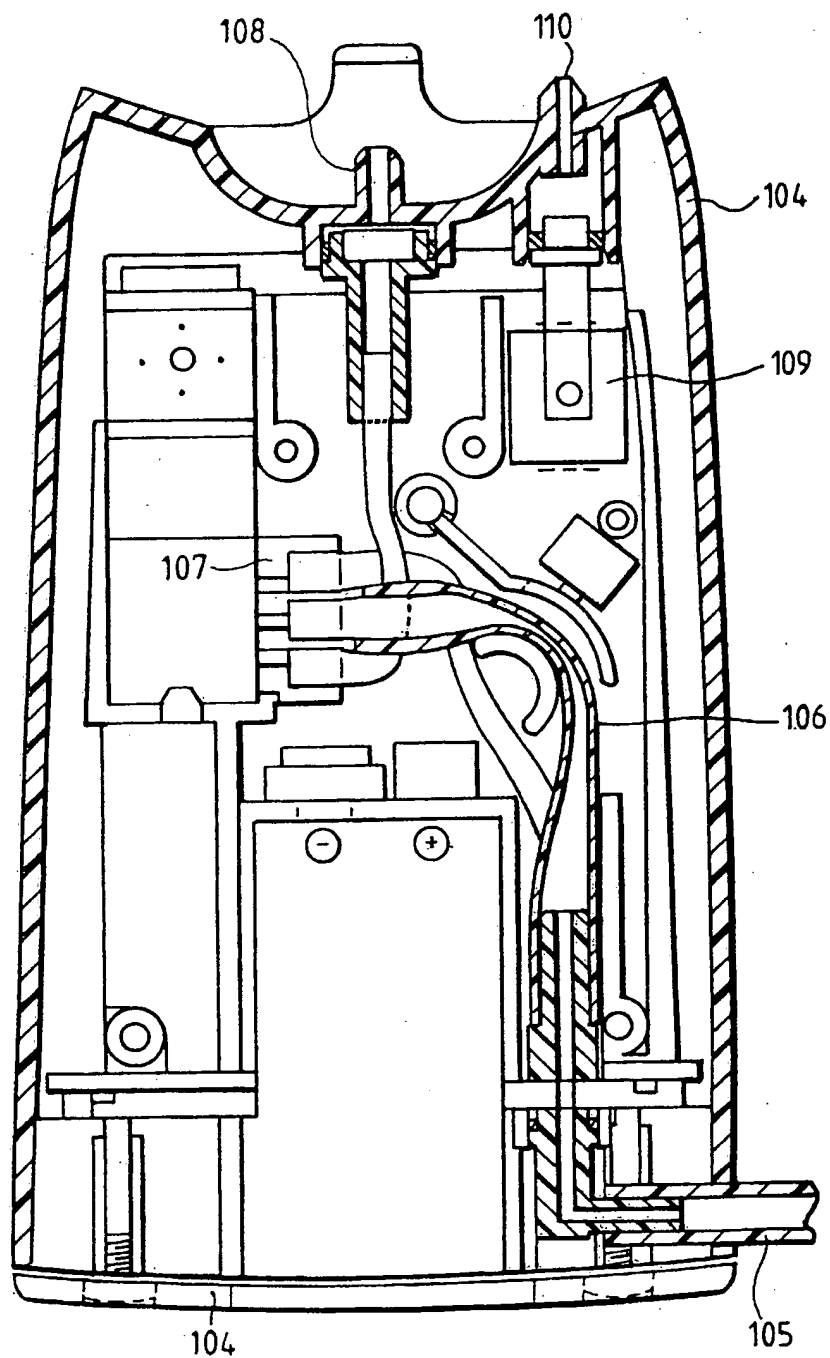


Fig.7.

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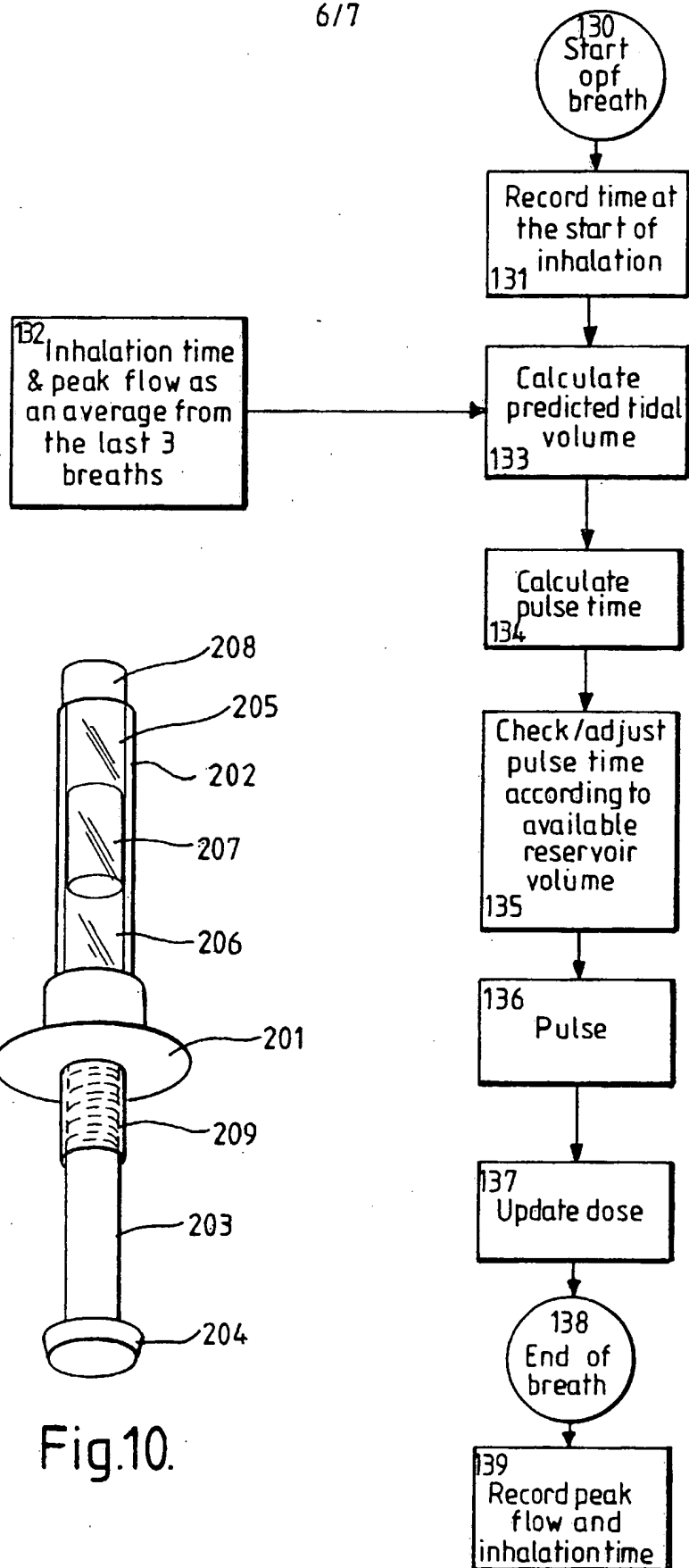


Fig. 8.

Fig. 10.

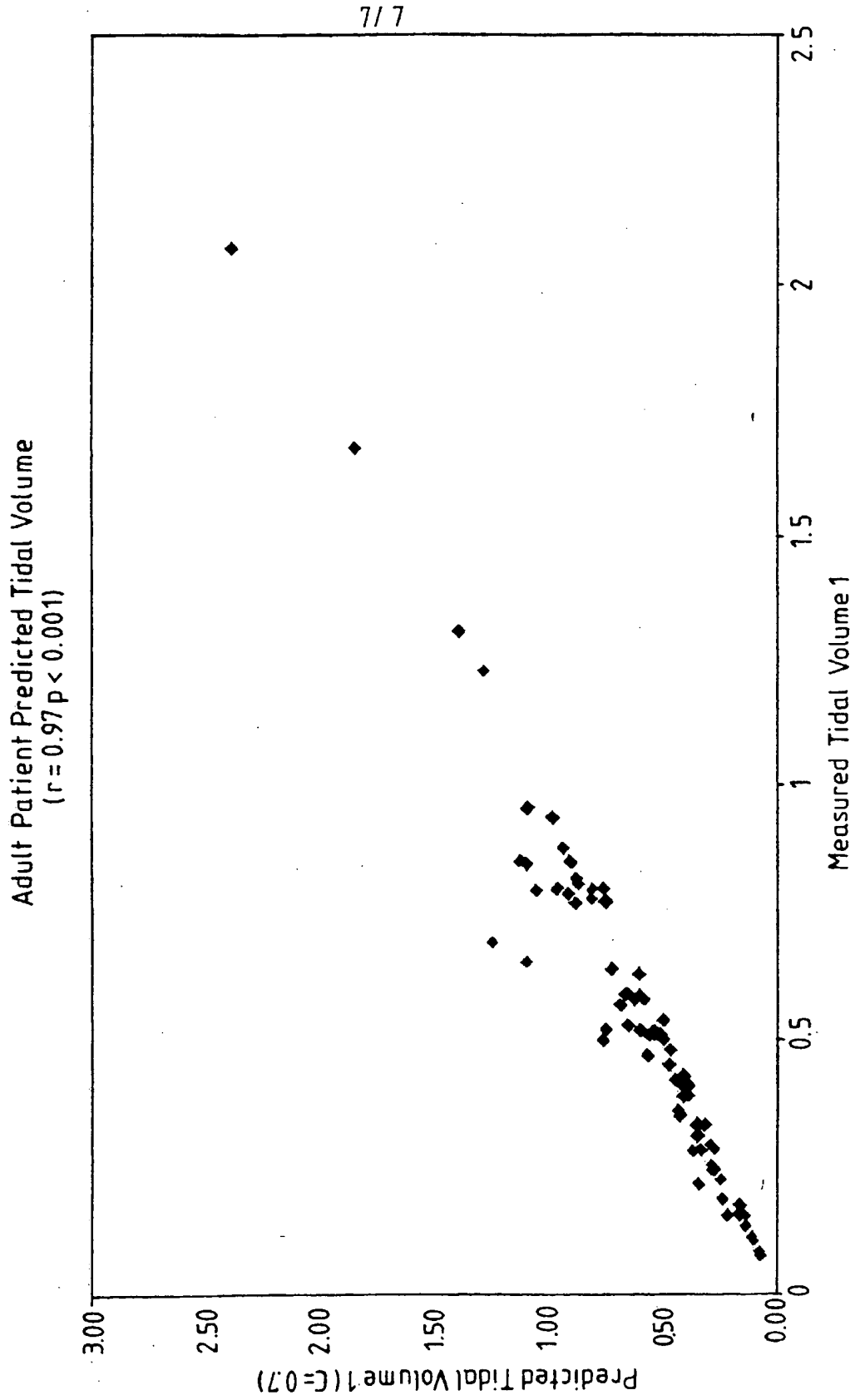


Fig.9.

INTERNATIONAL SEARCH REPORT

Internat. Application No.

PCT/US 01/04532

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61M15/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61M

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	GB 2 294 402 A (AID MEDIC LTD ;ASTRA AB (SE)) 1 May 1996 (1996-05-01) cited in the application page 5, line 6 -page 16, line 2; figures 1-16 ----	1-15
Y	WO 96 00595 A (BOEHRINGER INGELHEIM KG ;BOEHRINGER INGELHEIM INT (DE); NOEHL KLAU) 11 January 1996 (1996-01-11) page 3, last paragraph -page 4, paragraph 3; figures ----	1-15
A	GB 2 306 891 A (JONES JR WILLIAM CUNNINGHAM ;JONES SCOTT EDWARD (US)) 14 May 1997 (1997-05-14) page 6, last paragraph -page 7, paragraph 2; figure 5 -----	1,10,11

☐ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

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Date of the actual completion of the international search

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 01/04532

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
GB 2294402 A	01-05-1996	AT 192342 T	15-05-2000
		AU 691687 B	21-05-1998
		AU 3845595 A	23-05-1996
		BR 9509531 A	30-09-1997
		CA 2203805 A	09-05-1996
		CZ 9701261 A	15-10-1997
		DE 69516724 D	08-06-2000
		DK 802813 T	02-10-2000
		WO 9613294 A	09-05-1996
		EP 0802813 A	29-10-1997
		ES 2148573 T	16-10-2000
		FI 971791 A	25-04-1997
		HU 77163 A	02-03-1998
		JP 10509062 T	08-09-1998
		NO 971874 A	05-06-1997
		NZ 295172 A	28-10-1998
		PL 319942 A	01-09-1997
		PT 802813 T	31-10-2000
		RO 115406 B	28-02-2000
		SK 52897 A	08-10-1997
		US 5842468 A	01-12-1998
WO 9600595 A	11-01-1996	DE 4422710 C	14-09-1995
		AT 192659 T	15-05-2000
		AU 701504 B	28-01-1999
		AU 2886795 A	25-01-1996
		BR 9508137 A	04-11-1997
		CA 2193858 A	11-01-1996
		DE 59508328 D	15-06-2000
		DK 767683 T	09-10-2000
		EP 0767683 A	16-04-1997
		ES 2145281 T	01-07-2000
		JP 10501999 T	24-02-1998
		PT 767683 T	31-08-2000
		US 6119684 A	19-09-2000
		ZA 9505303 A	14-02-1996
GB 2306891 A	14-05-1997	US 5724986 A	10-03-1998
		AU 701769 B	04-02-1999
		AU 7061996 A	15-05-1997
		CA 2189683 A	07-05-1997
		GB 2340407 A,B	23-02-2000